UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/520,130	03/07/2000	Robert Arathoon	P1099R2	1353

25226 7590 01/22/2009
MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
01/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/520,130	ARATHOON ET AL.	
	Examiner	Art Unit	
	ANNE L. HOLLERAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 9/26/2008 is acknowledged. Claims 54-69 are pending and examined on the merits.

Claim Rejections Withdrawn:

Claim Objections

The objections to claims 57 and 64 because of informalities are withdrawn in view of the amendment to the claims.

Claim Rejections - 35 USC § 112

The rejection of claims 64-69 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to claim 64.

The rejection of claim 62 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn upon further consideration, and in view of applicants' arguments.

Claim Rejections Maintained and New Grounds of Rejection:

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 54-69 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 56-77 of copending Application No. 09/373,403. The rejection is maintained for the reasons of record.

Claims 54-69 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-82 of US Patent No. 7,183,076. This rejection was originally a provisional rejection over application no. 10/143,437. The rejection is maintained for the reasons of record.

Applicants have requested that the examiner hold these rejections in abeyance until notice of allowable subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-69 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons of record.

Applicants point to page 22, line 18 to page 23, line 5 and also to page 23, lines 5-9 for support of the invention of claims 64-69, which is drawn in part to bispecific antibodies having common light chains, where the common light chains are not identical in amino acid sequence to each other. Applicants states that common light chains identical to each other within the complementarity determining regions (CDRs) and different from each other outside of the CDRs are fully supported by the specification. Applicants also argue that it is basic claim construction principle that limitations from the specification may not be imported into the claims (CollegeNet, Inc. v. ApplyYourself, Inc., 418 F.3d 1225, 1231 (Fed Cir. 2005), and allege that the examiners' consideration that "there are instances in the specification that applicant conceived of methods of making bispecific antibodies where all the binding domains comprise a light chain having the same sequence.

Applicants' arguments have been carefully considered, but fail to persuade. The passages referred to by applicants, are passages describing processes for identification of useful light chains to be used as the common light chain of a bispecific antibody. The passages cited by applicant do not define the term "common light chain" to include light chains present in a

bispecific antibody where the two light chains are different in amino acid sequence. Therefore, the passages cited by applicant do not provide support for the claimed invention. With respect to the reference to CollegeNet, the examiner does not agree that the arguments made in the previous Office action are based on improper claim construction where a limitation from the specification is imported into a claim. The cited case law does not seem to be on point, because the issue in College Net, with respect to claim construction, has to do with whether a lower court had failed to properly construe a claim. The examiner has construed claims 64-69 to include bispecific antibodies where the two light chains are identical, or where the two light chains are not identical but are identical at least within the CDRs. This appears to be the correct claim construction. However, the disagreement between applicants and the examiner is not a matter of claim construction, but instead a matter of what is provided by the specification to support the invention as it is now claimed. The determination of whether a specification provides written description for a claim that is not an original claim requires an examination of the specification. In setting forth a rejection, the examiner must discuss what is found in the specification and what is not. Therefore, the rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 54 and 56 remain rejected under 35 U.S.C. 102(b) as being anticipated by de Kruif-A (de Kruif, J. et al. Journal of Biological Chemistry, 271(13): 7630-7634, 1996; cited in IDS) as evidenced by de Kruif-B (de Kruif, J. et al, J. Mol. Biol., 248: 97-105, 1995; cited in IDS).

The amendment to claim 54 broadens the scope of the previously present version of claim 54. Claim 54 as it now reads, encompasses bispecific antibodies that are dimeric scFvs, dimeric Fvs, and also a non-functional species having two heavy chains and only one light chain. The rejection is maintained because claim 54 continues to read on dimeric scFv molecules.

Applicants state that the dimerized scFv antibodies of de Kruif-A were derived from a library constructed from multiple light chains, and the libraries of Hoogenboom and Winter (1992) or Nissim (1994) that were mentioned were not the subject of either de Kruif-A or de Kruif-B. This is not found persuasive because, while de Kruif-A contained an example that did not encompass dimerized scFvs where the light chain in each of the scFv comprised the same amino acid sequence, de Kruif-A did provide the general teaching that in a method of making dimerized scFvs for the purpose of making bispecific immunoglobulins one could look to different examples of antibody libraries. It turns out that at least two of these suggested libraries were ones containing collections of heavy chain variable regions combined with one light chain variable region. The claims are broadly drawn to any bispecific antibody that may be a dimerized scFv where the amino acid sequences of the light chains are the same. In view of the broad scope of the claims, the rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 54, 55, 58-61, and 63 are rejected under 35 U.S.C. 103(a) as being obvious over Carter-B (WO 96/27011; published 6 Sep., 1996; cited in IDS) in view of de Kruif-A (de Kruif, J. et al. The Journal of Biological Chemistry, 271 (13): 7630-7634, 1996; cited in

IDS) and further in view of de Kruif-B (de Kruif, J. et al, J. Mol. Biol., 248: 97-105, 1995; cited in IDS).

The claims read on scFv dimers, where one of the binding domains binds one antigen and the other binding domain binds a second antigen (i.e. bispecific), and where the light chain variable domains of each of the binding domains are identical in sequence.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that the examiner has not established a prima facie case of obviousness based on an "obvious to try" rationale, and that the references do not teach or suggest all of the elements. With respect to teaching or suggesting each and every element of the claims, applicants state that the dimerized scFv antibodies of de Kruif-A were derived from a library constructed from multiple light chains, and the libraries of Hoogenboom and Winter (1992) or Nissim (1994) that were mentioned were not the subject of either de Kruif-A or de Kruif-B. This is not found persuasive because, while de Kruif-A contained an example that did not encompass dimerized scFvs where the light chain in each of the scFv comprised the same amino acid sequence, de Kruif-A did provide the general teaching that in a method of making dimerized scFvs for the purpose of making bispecific immunoglobulins one could look to different examples of antibody libraries. It turns out that at least two of these suggested libraries were ones containing collections of heavy chain variable regions combined with one light chain variable region.

With respect to an articulation of an "obvious to try" rationale, while the examiner did not set forth the arguments in exactly the manner that applicant does in the response, all of the information is provided by the rejection set forth in the previous Office action. Applicants state that the examiner must articulate a finding at the time of the invention that there had been a

recognized problem or need in the art which may include a design need or market pressure to solve a problem. The problem or need in the art was how to make bispecific antibodies efficiently. This was recognized by Carter-B in the teaching and suggestion of methods of making bispecific antibodies where formation of a heterodimer is favored over formation of a homodimer. Additionally, Carter-B recognized that two polypeptides making up the heterodimer could comprise scFv antibody fragments (page 10, lines 16-25, and lines 37-46; page 11, lines 17-24; and page 19, lines 2-7; page 21, lines 3-17; pointed to in previous Office action on page 9, lines 5-6). In the use of scFv antibody fragments in making bispecific antibodies, one may have two previously known parent antibodies, and clone out the appropriate regions to make the two scFv antibody fragments and use the light chain from each of the two parent antibodies. Alternatively, as taught by de Kruif-A, one could look to antibody fragment libraries as a source for the two binding sites of a bispecific antibody. Applicants make the statement that in view of de Kruif-A and de Kruif-B, a person of ordinary skill in the art would have no good reason to make the combination asserted by the examiner because according to de Kruif-A and de Kruif-B the construction of phage antibody libraries strongly favors large size and diversity achievable through the use of multiple light chains. However, the examiner has never argued that the references suggest to one to make phage antibody libraries with any particular characteristics. Instead the examiner argues that at the time of the invention, it appears that there were a finite number of such libraries and at least two of them were Hoogenboom and Winter (1992) library and the Nissim library (1994), which are libraries characterized by de Kruif-B as containing a collection of V_H genes combined with one V_L gene. Furthermore, de Kruif-A provides a suggestion for using these libraries. Given that de Kruif-A successfully made a bispecific

immunoglobulin using scFv antibody fragments, it appears that one of ordinary skill in the art could have pursued the suggestion to make a bispecific antibody using any of the suggested libraries with a reasonable expectation of success. Therefore, it was concluded in the previous Office action that it would have been obvious to try to use the methods of Carter-B (which encompassed making bispecific antibodies using scFv antibody fragments) to make dimerized scFv bispecific antibodies having a multimerization domain; and to obtain the scFv sequences from phage libraries as taught and suggested by de Kruif-A, which teaches a successful dimerization of scFvs to make a bispecific immunoglobulin, and to use one of the libraries suggested by de Kruif A, which would necessarily result in a bispecific immunoglobulin where each binding domain had the same light chain if one used the library of Hoogenboom and Winter or of Nissim. Because there appears to have been a finite number of libraries it appears that one could easily have chosen either of these libraries.

Additionally applicants argue that there is no motivation to make a restricted library, that the references teach away from the present invention, and that the examiner used improper hindsight in formulating the rejection. These arguments are not found persuasive because the rejection is not based on the argument that it would have been obvious to make a restricted scFv library. Instead the argument is based on the fact that such libraries already existed at the time filing, and that the prior art contained a suggestion to use such libraries. With respect to improper hindsight, applicants state that the examiner picked and chose selected portions of Carter-B which were then combined with de Kruif-A and de Kruif-B in an attempt to recreate the claimed invention. This is not the case at all. To show which elements of the invention were provided by Carter-B, the examiner pointed to various positions in the document to show where

specific teachings of claim limitations were to be found. The next question to answer was if in practicing a specific embodiment of Carter-B (use of scFv fragments in making a bispecific antibody), there was any further guidance in the prior art. The examiner found such guidance in de Kruif-A, and used de Kruif-B to understand the nature of scFv libraries suggested by de Kruif-A. Because de Kruif-A successfully uses an scFv library to make a bispecific antibody and because de Kruif-A points to specific libraries as sources for scFv sequences, the examiner concluded it would be obvious to try to make bispecific antibodies of Carter-B with the libraries of de Kruif A, where using at least two of them would necessarily result in structures that are the same as those made by claimed methods.

Claims 54, 56-60 and 63 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hu (Hu, S.-z., et al., Cancer Research, 56: 3053-3061, 1996; cited in the IDS) in view of de Kruif-A (supra) and further in view of de Kruif-B (supra).

The claims encompass bispecific antibodies comprising multimerization domains that are made up of a domain from a constant region of an antibody and also a non-naturally occurring disulfide bond, where the antigen binding domains are made of scFv fragments, where one scFv binds one antigen and the other scFv binds a second antigen.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that the examiner cites references that do not teach or suggest all of the elements in the claims, that the examiner fails to articulate an "obvious to try" rationale, that the references teach away from the present invention, and the examiner uses improper hindsight in formulating the rejection. These are arguments that are essentially the same as those presented for the rejection

above. Applicants make the statement that one of ordinary skill in the art would have no good reason to make the combination asserted by the examiner because the minibodies of Hu were constructed by dimerizing a specific scFv using CH3 domains, and that the protocol of Hu requires selection of a distinct scFv, whereas if the examiner's asserted combination were to be following, two distinct scFv molecules would have to be selected from a library such as the one described in de Kruif-B. Applicants go on to say that there is no good reason to reduce the number of light chains from seven to one in the de Kruif-B library in an attempt to identify suitable scFv molecules for use with the protocols of Hu. Applicants' arguments are not persuasive because the teachings of Hu are a teaching for how to dimerize two heavy chains from two different scFv molecules, which is desired whether one is making a bivalent, monospecific antibody species, or bispecific antibody species, which each binding domain binding to a different antigen by monovalent binding. Hu is silent on using the method to make bispecific antibodies. However, the teachings of de Kruif-A and de Kruif-B can be combined with the teachings of Hu, because de Kruif-A demonstrates that scFv fragments may be assembled together to make bispecific antibodies, and because de Kruif-A teaches that a source of scFv fragments for assembling such bispecific antibodies may be phage antibody libraries, which happen to include libraries where the different scFv molecules all comprise a light chain variable domain that has the same amino acid sequence. Applicants have not shown why it would be unexpected or unreasonable to use Hu's dimerization method to make bispecific antibodies. With respect to combining Hu with de Kruif-A and de Kruif-B applicant states that there is no good reason to make this combination. The examiner disagrees because de Kruif-A specifically teaches that using antibody phage libraries in methods of making bispecific

antibodies, and specifically teaches examples of libraries to use as a source of scFv sequences. Therefore, for the reasons set forth above, applicants' arguments are not convincing and the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the

status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
January 14, 2009
/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643